



## EDITORIAL

# Steroidal Substances Active in the Human Vomeronasal Organ Affect Hypothalamic Function

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We now have conclusive evidence that the hypothalamus serves as a link between the vomeronasal organ (VNO) and the endocrine system in human beings and also that the VNO acts as an additional sensory system (sixth sense) which affects psycho-physiological homeostasis, as well as autonomic reflexes.

It is known that terrestrial animals have a functional VNO which responds to pheromones of conspecifics and that the destruction of the VNO in prepubertal animals severely impairs sexual behavioral activity. However, the human VNO has been thought to be only sporadically present, and to be an inactive non-functional vestigial organ. Various scientists (Drs Nathan W. Adams, Augusto Bondani, Clive Jennings-White, Luis Monti-Bloch) and scientific advisors (Drs Vicente Diaz-Sanchez, Bernard I. Grosser, David T. Moran, Larry J. Stensaas, Jose Garcia-Velasco) at Pherin Corporation (Menlo Park, CA, U.S.A.) have demonstrated that the human VNO exists on both sides of the nasal septum of all normal adults, males and females (more than 1500 subjects studied). We have also shown that the human VNO is physiologically responsive to certain substances, defined as vomeropherins.\* In 1991 an international symposium on pheromones was held in Paris and the proceedings were published in *The Journal of Steroid Biochemistry and Molecular Biology* Vol. 39, No. 4B, pp. 545-680, 1991. During this symposium, we introduced for the first time scientific data that demonstrated that the human VNO is functional.

The VNO is connected to the brain through its hypothalamic and limbic neural connections. Vomeropherins activate chemosensory cells in the vomeronasal organ, which in turn transmit neural impulses to the

hypothalamus. By regulating hypothalamic function in this way, it is possible to modulate autonomic, psycho-physiological and hormonal responses. Signal transduction through the VNO receptors provides site-specific neural transmission to the brain. The hypothalamus controls such basic functions as anger, fear, anxiety, aggression, heart rate and blood pressure, body temperature, sugar and fat metabolism, water and electrolyte balance, appetite, sexual motivation, and the hormonal system.

Over 100 novel chemosensory substances, which we have termed "vomeropherins" and for which patent applications have been submitted, have been synthesized in our laboratories (one of the major patents has recently been allowed). These substances produce a physiological and pharmacological effect in the VNO. It is interesting to note that some vomeropherins have a gender-specific effect in the human VNO and consequently in the hypothalamus.

Significant changes in autonomic function were observed after application to the VNO of small concentrations ( $10^{-9}$ - $10^{-15}$  M) of vomeropherins. Among the observations for one class of vomeropherins were: (a) reduction of cardiac and respiratory rate; (b) increase in body temperature; (c) increase in the electrical conductance of the skin (galvanic skin response); and (d) increase in alpha-rhythm brain waves. Concurrent with these changes, an increase in parasympathetic tone and an amelioration of anxiety effects were also observed. Additionally, pharmacodynamic studies have demonstrated that certain steroidal vomeropherins, when delivered to the VNO, influence the hypothalamic pituitary system by producing significant changes in plasma concentration of luteinizing hormone (LH) and follicular stimulating hormone (FSH) in humans.

In recent studies we have demonstrated that picogram quantities of vomeropherins are effective, and

\*VOMERO: vomeronasal organ; PHERIN: to convey or deliver—substances that stimulate or send messages through the VNO, e.g. mammalian pheromones are naturally occurring species-specific vomeropherins.

we have invented a patented application device to deliver these substances to the VNO. From these developments it is clear that the advantages of vomeropherins as therapeutic agents include both safety and efficacy. Specifically, vomeropherins are: (a) effectively non-toxic; (b) active in picogram quantities; (c) without systemic involvement; (d) with specificity of action; (e) with rapid onset; and (f) easily dosed with a special nasal device.

Because of their direct effect on the hypothalamus

through neural transmission, the potential therapeutic uses of vomeropherins are enormous. To speculate, the medical treatments which could benefit in the foreseeable future are: generalized anxiety (acute panic attacks and social phobias); other central nervous system (CNS) disorders; cancer therapy (prostate and breast cancers); hormone replacement therapy; premenstrual syndrome therapy; fertility control; appetite control; sexual dysfunction, etc.